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Caspase-1 expression in multiple sclerosis plaques and cultured glial cells

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Abstract

Caspase-1 is responsible for processing inflammatory cytokines and is associated with the induction of apoptosis. Using RT-PCR, we found that caspase-1 mRNA transcripts from frozen brain extracts were significantly elevated in multiple sclerosis (MS) compared to controls. Immunohistochemical staining using a specific antiserum confirmed the marked up regulation of caspase-1 within acute and chronic MS plaques, while little staining was seen in control brains. In addition to the expected caspase-1 expression in microglia and infiltrating perivascular mononuclear cells, we found that cytoplasmic caspase-1 expression was sharply increased in the resident oligodendrocytes of MS lesions. The TUNEL reaction for fragmented DNA co-localized over an occasional caspase-1-expressing cell and large numbers of caspase-1-positive "corpses" were observed within phagocytic macrophages of an acute evolving MS lesion. Studies using an immortalized human oligodendroglial hybrid cell line exposed to cytokine challenge showed that death induction was blocked by the caspase-1-like inhibitor Z-YVAD-fmk, while the caspase-3-like inhibitor Z-DEVD-fmk was less effective. Cellular levels of procaspase-1 were reduced compared to controls in oligodendroglia induced to die by cytokine challenge, as judged by Western immunoblotting. Our results suggest that caspase-1 may play a role in the inflammatory and apoptotic processes associated with MS pathogenesis.

Keywords: Caspase-1; Multiple sclerosis; Plaques; Oligodendrocyte; Cultures

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease and its neuropathology is characterized by CNS white matter plaques displaying myelin loss and gliosis [1,2]. Inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β), and interferon-gamma (IFN-γ) are upregulated in MS plaques [3], although the precise link between the inflammatory process and myelin sheath destruction is unclear. In previous investigations on the fate of glial cells, we identified substantial numbers of apoptotic oligodendrocytes within developing and mature MS lesions by the in situ TUNEL reaction [4,5]. We also found that glial cells in MS plaques often strongly express both Fas receptor and ligand on their plasma membrane surface, suggesting that the Fas death pathway may be active during MS lesion formation [6]. However, the precise molecules and intracellular pathways responsible for glial cell death in MS remain ill-defined.

Caspase-1, previously named interleukin-1β converting enzyme (ICE), is a cysteine protease whose proteolytic activity makes it a key molecule in myriad cellular processes, including mediation of the inflammatory response through cleavage activation of IL-1β and IFN-γ promolecules. In addition, developmental studies in the nematode *C. elegans* have shown that the caspase-1 homolog CED-3 is chief among the genes required to induce programmed cell death [7–9]. We investigated caspase-1 expression in MS white matter lesions and tested for its activation in response to death induction by cytokine stimulation on immortalized cultures of oligodendrocytes.

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